

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

|                                 |   |                           |
|---------------------------------|---|---------------------------|
| In re Application of            | ) |                           |
|                                 | ) |                           |
| Tim M. TOWNES et al.            | ) | Art Unit: 1632            |
|                                 | ) |                           |
| Application No. 10/659,675      | ) | Examiner: Lietto, Louis D |
|                                 | ) |                           |
| Filing Date: September 10, 2003 | ) | Confirmation No. 3735     |
|                                 | ) |                           |
| For: "TRANSGENIC ANIMALS THAT   | ) |                           |
| PRODUCE HUMAN HEMOGLOBIN"       | ) |                           |

**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

**Mail Stop AF**  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.  
Customer Number 23859

Dear Sir:

Applicants request "Pre-Appeal Brief Request for Review" of the final rejection in the above identified application mailed April 21, 2006. No amendments are being filed with this Request. This request is being filed in conjunction with a Notice of Appeal, enclosed herewith.

The review is requested for the reasons stated in the Remarks. The Remarks have been limited to five or fewer pages, not including this cover sheet, in accordance with the OG Notice issued 12 July 2005.

**Remarks**

Claims 1, 2, 4-19, 21, 22, and 23 are pending.

**Rejection Under 35 U.S.C. § 112, first paragraph**

The Examiner is not applying the correct standard for enablement.

In the final rejection mailed April 21, 2006, the Examiner asserted that “the specification ... does not reasonably provide enablement for a transgenic mouse comprising erythrocytes that produce human hemoglobin without a switch locus, but fail to produce adult hemoglobin endogenous to said nonhuman mammal.” (emphasis added). However, the Examiner actually appears to be arguing that since the claims broadly encompass a mouse comprising human sickling hemoglobin, the claim must also recite the switching construct required to make sickling mice.

First, the specification does not teach that the switching construct is necessary to produce a sickling mouse. What the specification does teach is that “a comprehensive mouse model of sickle cell disease would mimic the temporal switch of hemoglobins in man” and that a delay in hemoglobin switching to approximate the fetal to adult globin gene switch in man would increase viability of the mice (see paragraph 87). The specification provides a switching construct that satisfies this particular desired result. However, such a switching construct is not clearly required to produce a mouse expressing human hemoglobin (sickling or otherwise) without expressing endogenous adult hemoglobin.

Second, the Examiner is stating that the “specification” is not enabling because a member of the claimed genus (i.e., sickling mouse) requires an additional limitation (i.e., a switching construct) in order to be functional. This would be a valid argument if the specification did not disclose how to make and use the necessary construct. However, the Examiner is actually indicating that the Applicant should amend the claim to recite the specific LCR  $\gamma$ - $\beta$  hemoglobin switching DNA construct that is allegedly necessary to produce sickling mouse. However, such a requirement is not consistent with the enablement requirement, because if the specification discloses the switching construct, then it has taught how to make and use a sickling mouse regardless of whether the limitation is included in the claim. It should be noted that the Examiner makes the closing statement that “[n]either the specification, nor the declaration of Dr. Townes provides any support for such mice.” This statement is not in accordance with the Examiner’s

*Response To Arguments.* The Examiner does not appear to be making the clearly erroneous argument that the switching construct is not disclosed or enabled in the specification. Rather, the Examiner is apparently positing that the claim must recite the allegedly necessary limitation to enable a sickling mouse encompassed by the claims. However, as correctly pointed out by the Examiner, the “specification must teach those of skill in the art how to make and how to use the invention as broadly claimed” (emphasis added). Amending the claim to add the allegedly necessary construct does not comport with this requirement. The Applicant therefore respectfully requests the withdrawal of this rejection.

### **Rejection Under 35 U.S.C. § 103**

The Examiner rebutted evidence provided by the Applicants in the form of a declaration with unsupported statements based on hindsight.

In the final rejection mailed April 21, 2006, claims 1-19 were rejected under 35 U.S.C. § 103 for allegedly being unpatentable over Paszty et al., “Lethal  $\alpha$ -thalassaemia created by gene targeting in mice and its genetic rescue,” Nat Genet., 11(1):33-9 (1995) (“Paszty”), and Ciavatta et al. “Mouse model of human  $\beta^0$  thalassemia: targeted deletion of the mouse  $\beta^{\text{maj}}$  - and  $\beta^{\text{min}}$ -globin genes in embryonic stem cells,” Proc. Natl. Aced. Sci. USA 92:9259-9263 (1995) (“Ciavatta”) taken with Rubin et al., “Hypoxia-induced in vivo sickling of transgenic mouse red cells,” J. Clin. Invest., 87:639-47 (1991) (“Rubin”), and Fabry et al. “A second generation transgenic mouse model expressing both hemoglobin S (HbS) and HbS-Antilles results in increased phenotypic severity,” Blood, 86:2419-28 (1995) (“Fabry”). And, claims 21-24 were rejected under 35 U.S.C. § 103 for allegedly being unpatentable over Paszty and Ciavatta taken with Rubin and Fabry in further view of Westphal, “Tansgenic mammals and biotechnology,” FASEB J., 3(2):117-20 (1989) (“Westphal”).

In the response filed February 9, 2006, the Applicant argued that a *prima facie* case of obviousness had not been provided because no motivation in any of the cited references, or in the art as a whole, has been provided. The Examiner’s response was to indicate in the art a long-felt need for mouse models of human hemoglobin related disease and a recognition in the art of problems relating to the presence of mouse hemoglobins. At best, this combination provides a motivation to try to make the claimed invention (i.e., a mouse expressing human hemoglobin but not expressing mouse hemoglobin). However, a motivation to try is not sufficient. A *prima facie*

case of obviousness has not been provided because no motivation in any of the cited references, or in the art as a whole, has been provided.

Furthermore, the long felt need is actually evidence that there was actually no indication in the art that such a combination would be successful. Thus, even if, *arguendo*, there had been a motivation to combine the above references to make the claimed animals by mating the mice of Ciavatta and Paszty together, those of skill in the art would not have had a reasonable expectation of success that the claimed mammals would live. To this end, the Applicant provided a declaration by Dr. Townes indicating that one of skill in the art would not have predicted that a mouse could survive on human hemoglobin alone. Dr. Townes states,

“The production of mice that survive on human hemoglobin is predictive of the survival of larger mammals. The physiology of the mouse is more different from humans than is the physiology of the cow or sheep and humans. The high metabolic rate of the mouse requires efficient oxygen delivery and the oxygen affinity of mouse and humans are significantly different. Therefore, we could not predict that the mouse would survive on human hemoglobin. However, the fact that mice did survive exclusively on human hemoglobin makes it likely that large animals would also survive solely on human hemoglobin.” (Townes Declaration).

The Examiner rebutted this declaration with the assertion that the ordinary practitioner in the art would have expected mice to survive on human hemoglobin because they have higher levels of 2,3-diphosphoglycerate (DPG) than do humans, which allegedly change the binding affinity of hemoglobin to favor the metabolic environment of small animals. While it is possible that DPG levels contributed to the Applicants’ results, this fact alone is not sufficient to establish a *prima facie* case of obviousness or rebut the Applicants’ assertion of unexpected results. In order to support the Examiner’s position that a skilled artisan would have expected a mouse to survive on human hemoglobin alone, the predictive value of the alleged facts regarding DPG would have had to have been known prior to the Applicants’ priority date. However, no evidence was provided that the skilled artisan could have used this knowledge to predict the survival of small animals such as mice on human hemoglobin or that there would have been a reasonable expectation of success based on this prediction.

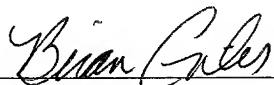
At best, the Examiner is combining unsupported facts with impermissible hindsight by taking the inventor’s disclosure as a blueprint for piecing together the prior art in an effort to defeat patentability. To avoid the impermissible error of hindsight reconstruction, a specific and

direct suggestion or motivation to alter the prior art to arrive at applicants invention must be present or apparent from the prior art; it cannot be merely a conclusion of the examiner. In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (to reject an inventor's claim for obviousness in view of a combination of prior art references, a showing of a suggestion, teaching, or motivation must be "clear and particular."). For at least this reason, the current rejection is legally flawed.

In addition, the Examiner's assertion that DPG levels in mice was known and predictive of survival on human hemoglobin is not consistent with the Applicants' evidence of long-felt need. Many of the techniques needed to make and use the claimed transgenic animals were present in the art for years before Applicants' application, but those skilled in the art lacked the expectation of success that a non-human mammal could live on human hemoglobin alone. For this and the reasons explained above, the Applicant respectfully requests the withdrawal of this rejection.

An electronic payment in the amount of \$760.00, representing \$250.00 for the Appeal fee pursuant to 37 C.F.R. §41.20(b)(1) and \$510.00 for the fee under 37 C.F.R. § 1.17(a)(3) for a Request for Three Month Extension of Time, is included herewith. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,  
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